

INDIANA UNIVERSITY

BLOOMINGTON, INDIANA

DEPARTMENT OF ZOOLOGY

Sept. 5, 1956

Dr. Joshua Lederberg
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Dear Dr. Lederberg:

Thank you for your most interesting letter of August 19. Your story about the cistrons in the Gal region is fascinating. It fits in with the idea (which I regard as a certainty) that different cases of pseudoallelism represent fundamentally different situations, of at least three kinds: (1) cases where one original gene got duplicated or further multiplied in situ (linearly, of course), (2) cases of position effect between genes that were not more closely related genetically than two genes taken at random ordinarily are, (3) cases of mutation at two different places within the same gene or locus. The term gene or locus could of course not be precisely defined here but it would have to be assumed that there were units that were separable at least functionally, if not structurally.

As you have noted, I tend to favor the view that there is a structural basis corresponding to the functional separation, although I am not wedded to the idea. I realize the limitations of my study of the scute region, and have given them in more detail in a paper of 1940 (the section beginning on page 569) than in my paper in the Brookhaven Symposium. Unfortunately I have only my own (last) copy left of the 1940 paper so although I am sending it to you, under separate cover, I am having to ask you to return it when you are finished with it. I am sending at the same time a copy of one of my 1935 papers on the subject, which you may keep. In 1936 I had the study in extenso, as it was up to that time, practically all written up. but it lacked just a few finishing touches that I never had time to get around to, and since then it has become one of those pieces of work, of which I have not a few lying around, on which I have so much data that I cannot get the papers out without neglecting the current projects on which my grants depend. In the meantime however the work with micro-organisms is forging so far ahead there is not much loss in not reviving these matters of ancient history. I should not be surprised however if bacteria differed from Drosophila and mammals in oftener having two-break structural *changes* that had each of their breaks within (different) "genes" or, to put the thing less paradoxically, if ~~at~~ the "higher" animals (and probably also plants, judging by maize) had their genetic material more distinctly segmented, with a sharper distinction between intergenic and intragenic mutations.

As for what Demerec said, you can find it by looking up his paper in the Brookhaven Symposium on Mutation, especially on pages 82-83. You will also be interested in the discussion following that paper, on pages 84-87. Incidentally, I believe that the last paragraph of his paper, on page 83, was added later, after he had had the benefit of that discussion, since I do not remember his presenting that at the time and if he had done so a considerable part of the discussion would have been superfluous. To answer your question more directly however, Demerec did not actually speak of a position effect ~~but~~ directly, but he did say that (following a suggestion that I believe he said was made by Wright but that does not appear credited to anyone else in his paper as published)

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he concluded that the arrangement of genes was of advantage to the organisms. Surely the arrangement could not be of advantage unless there were different effects given by that arrangement than by some other arrangement, that is, ~~a~~ position effects. In other words (and I think it is a perfectly legitimate inference and one that Demerec by himself would not have arrived at) it can be inferred from the fact that this arrangement has persisted that it has advantageous position effects. Otherwise it would in the long course of evolution have become scrambled. Furthermore, it can be calculated (although Demerec did not do this) that the chance of having two groups of loci (one concerned with tryptophane and the other with histidine), each consisting of four parts, both arranged linearly in the same order as that of the biochemical steps, is only one in 144. It was this consideration that led me to say that I thought the evidence for position effect here being dependent upon the local concentration of gene products was conclusive.

Jim Crow has written me that you were responsible for some important improvements in the manuscript by Morton, Crow and myself that we recently submitted to PNAS. I want to thank you for this. I feel pleased about this paper, especially in its latest form, ~~especially~~ as I think it opens up means of getting quantitative evidence concerning questions which till now have been on a pretty speculative and discursive basis, in which much wishful thinking has been carried on in opposite directions by opposed groups.

With kind personal regards,

Yours sincerely,



H. J. Muller

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